



Docket No.: ISIS-4853 Sheet 1 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 1

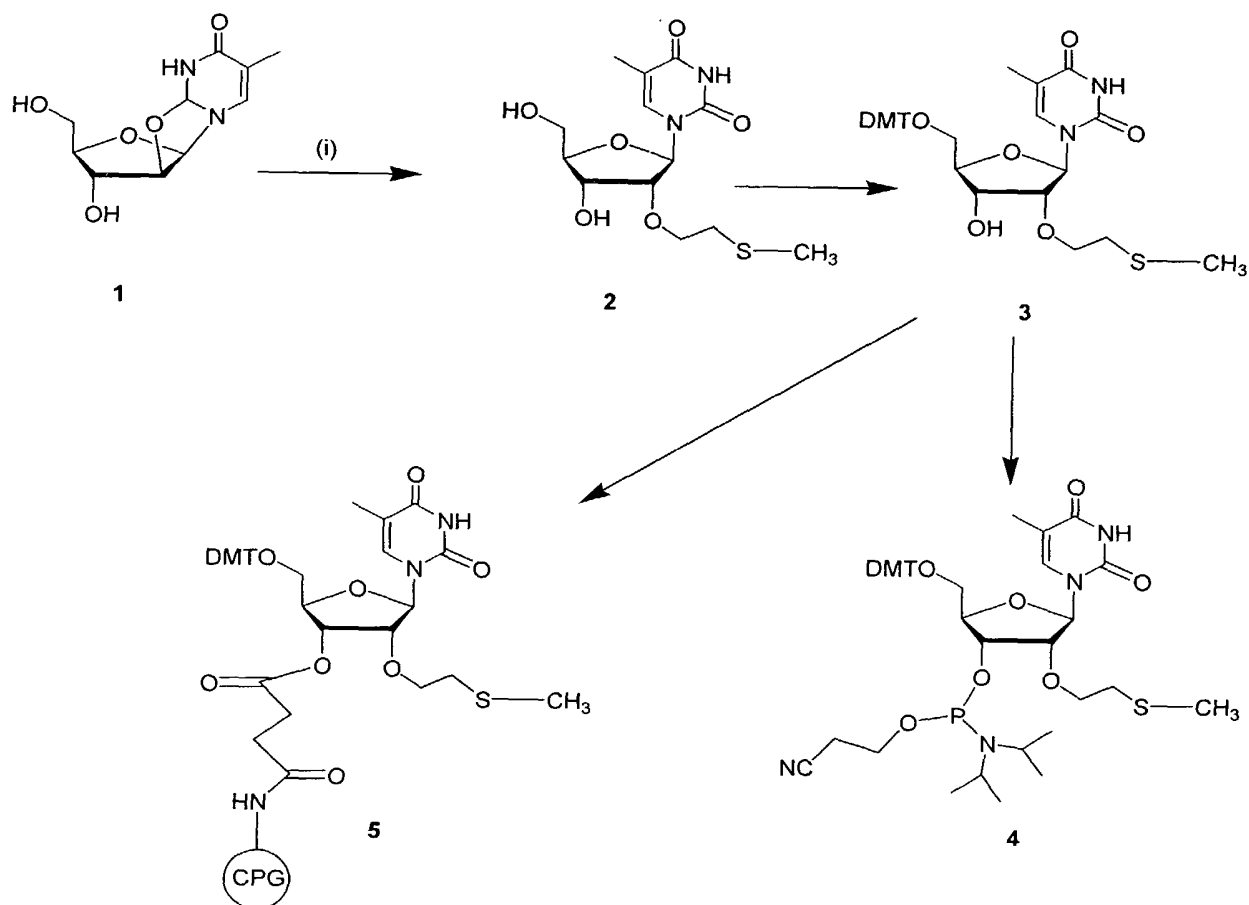
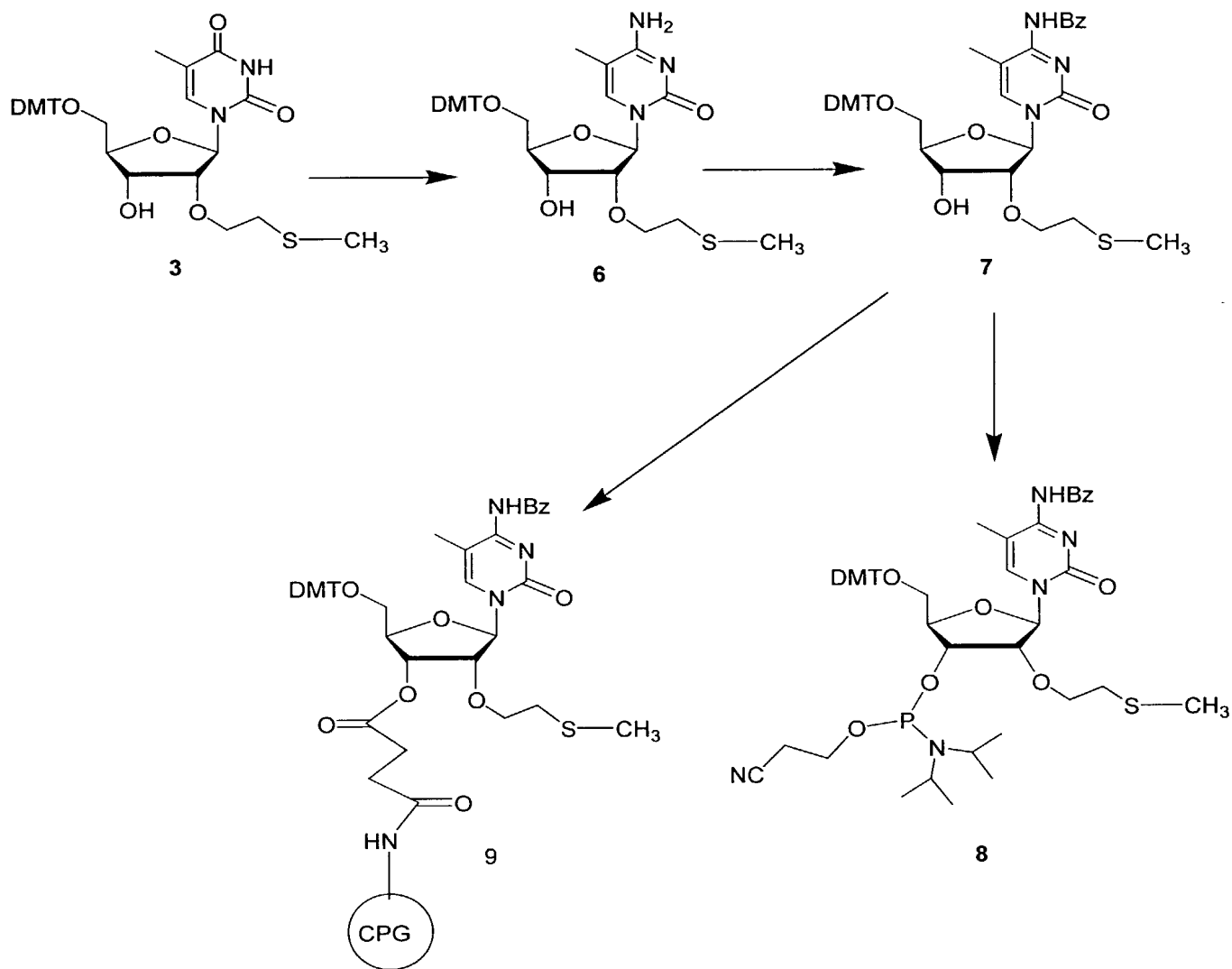




Figure 2





Docket No.: ISIS-4853

Sheet 3 of 28

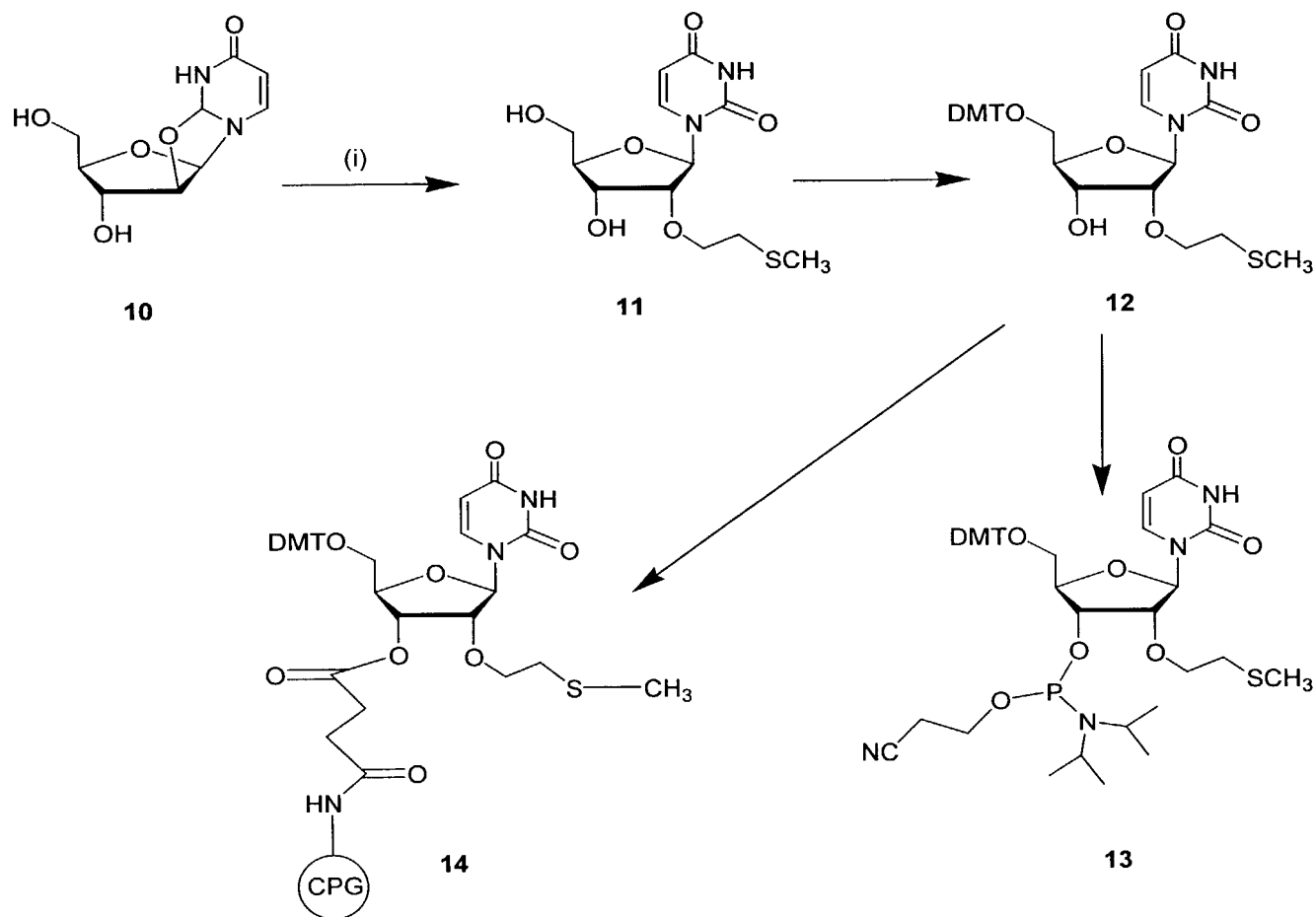
Title: Methods of Modulating Pharmacokinetics of Oligonucleotides

Inventors: Prakash and Manoharan

S/N: 10/058,740

Filing Date: 1/28/02

Figure 3





100587403, OFFICIAL

Docket No.: ISIS-4853 Sheet 4 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N. 10/058,740 Filing Date: 1/28/02

Figure 4

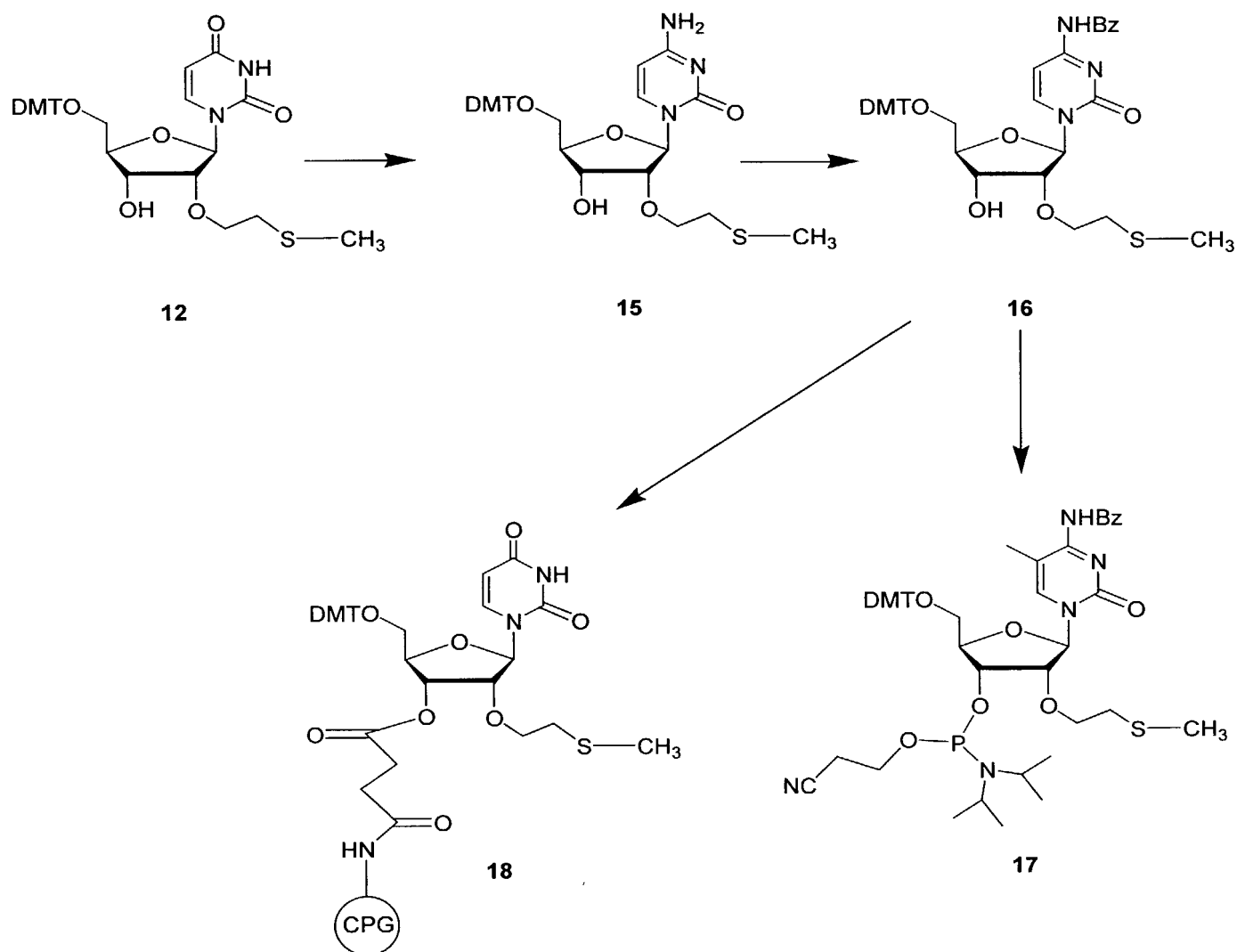




Figure 5

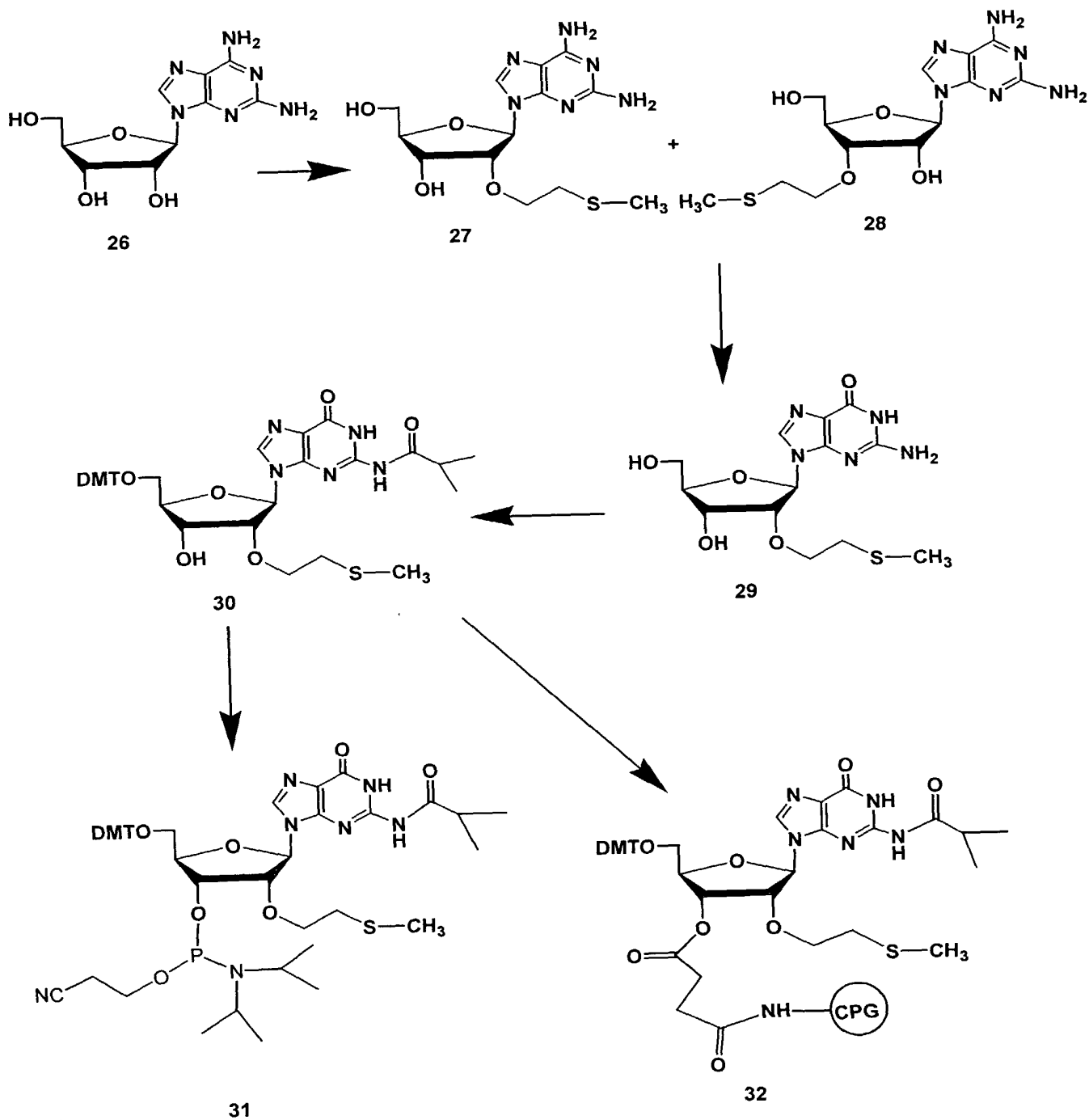




Figure 6

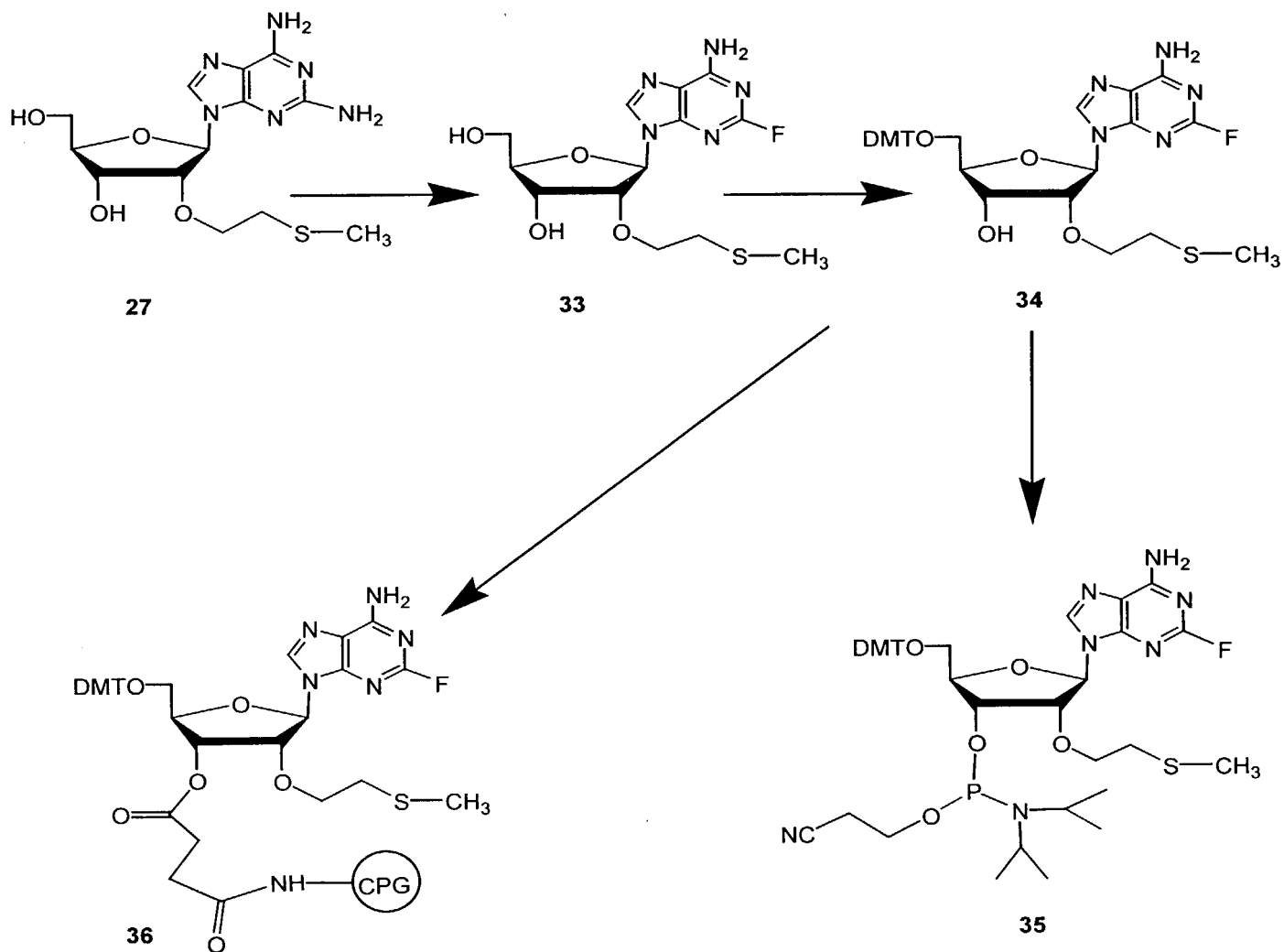




Figure 7

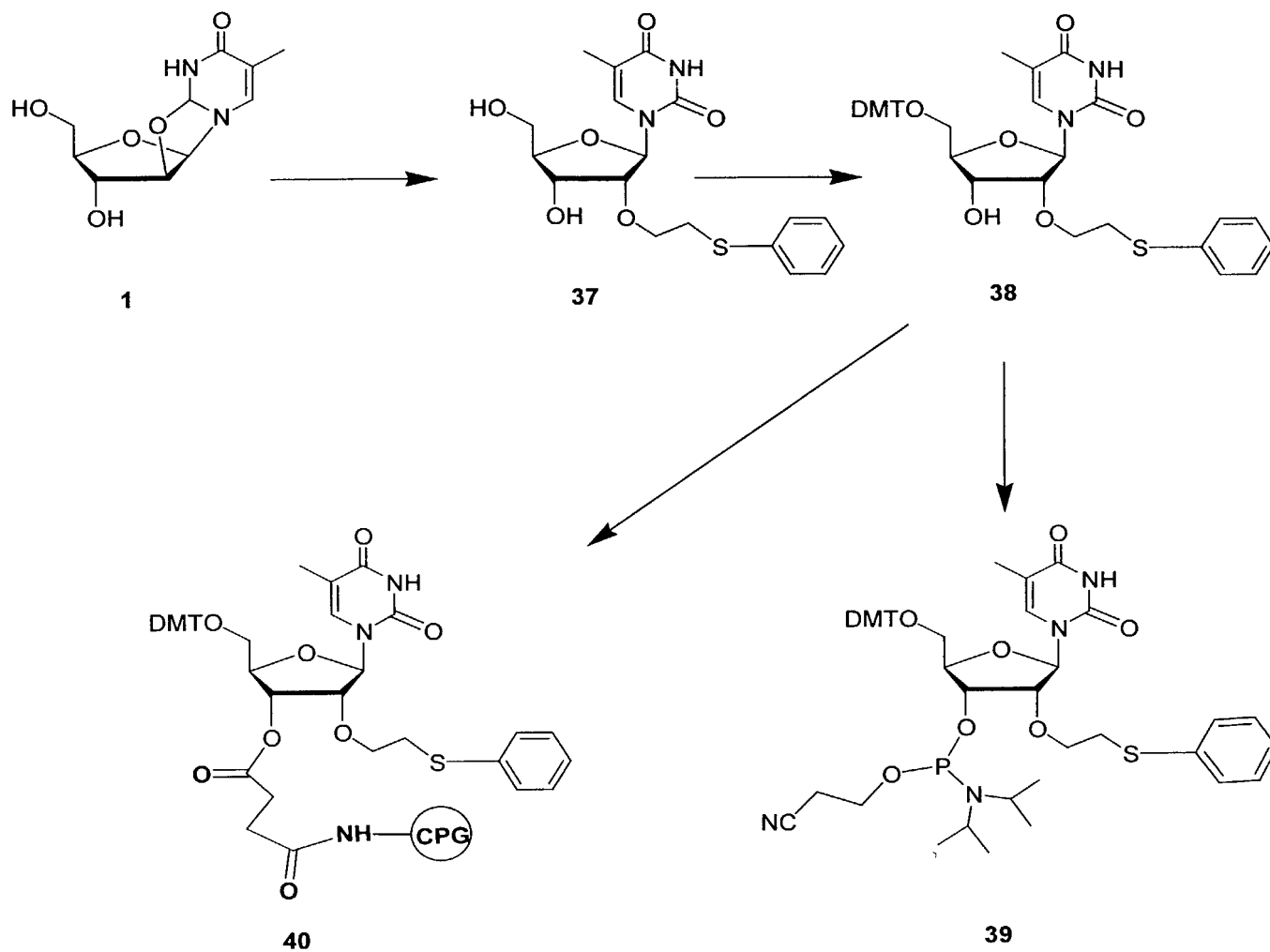




Figure 8

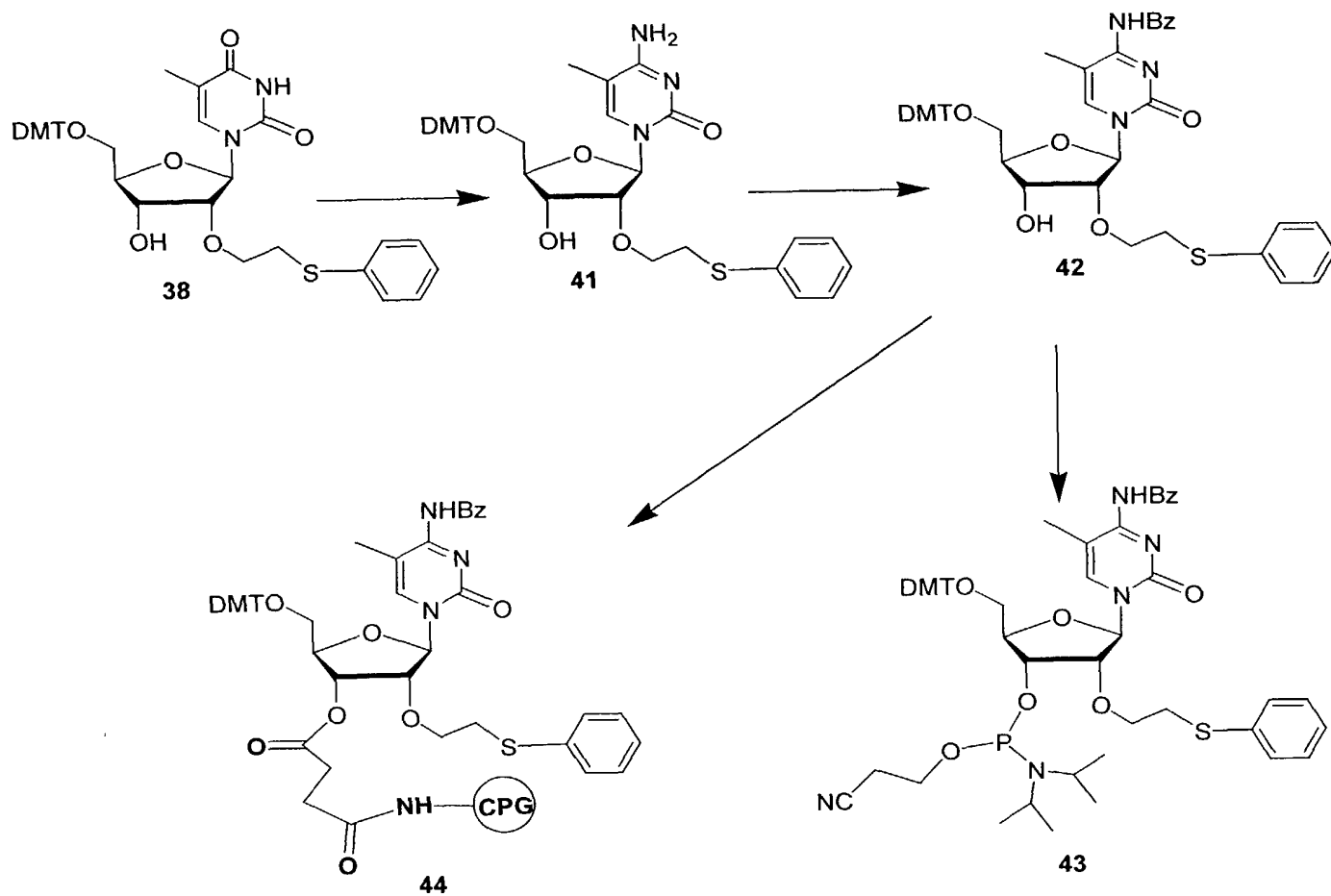




Figure 9

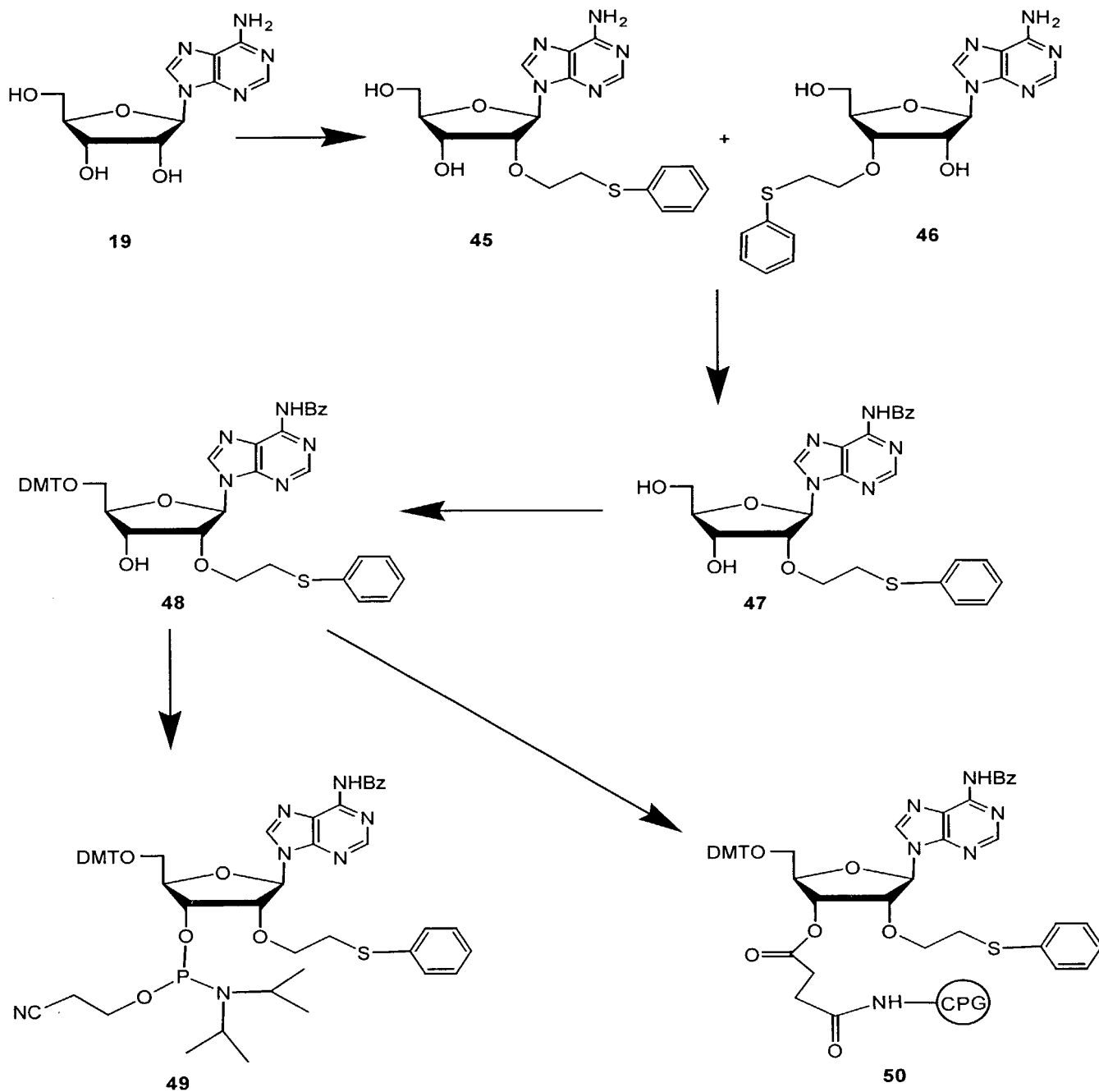




Figure 10

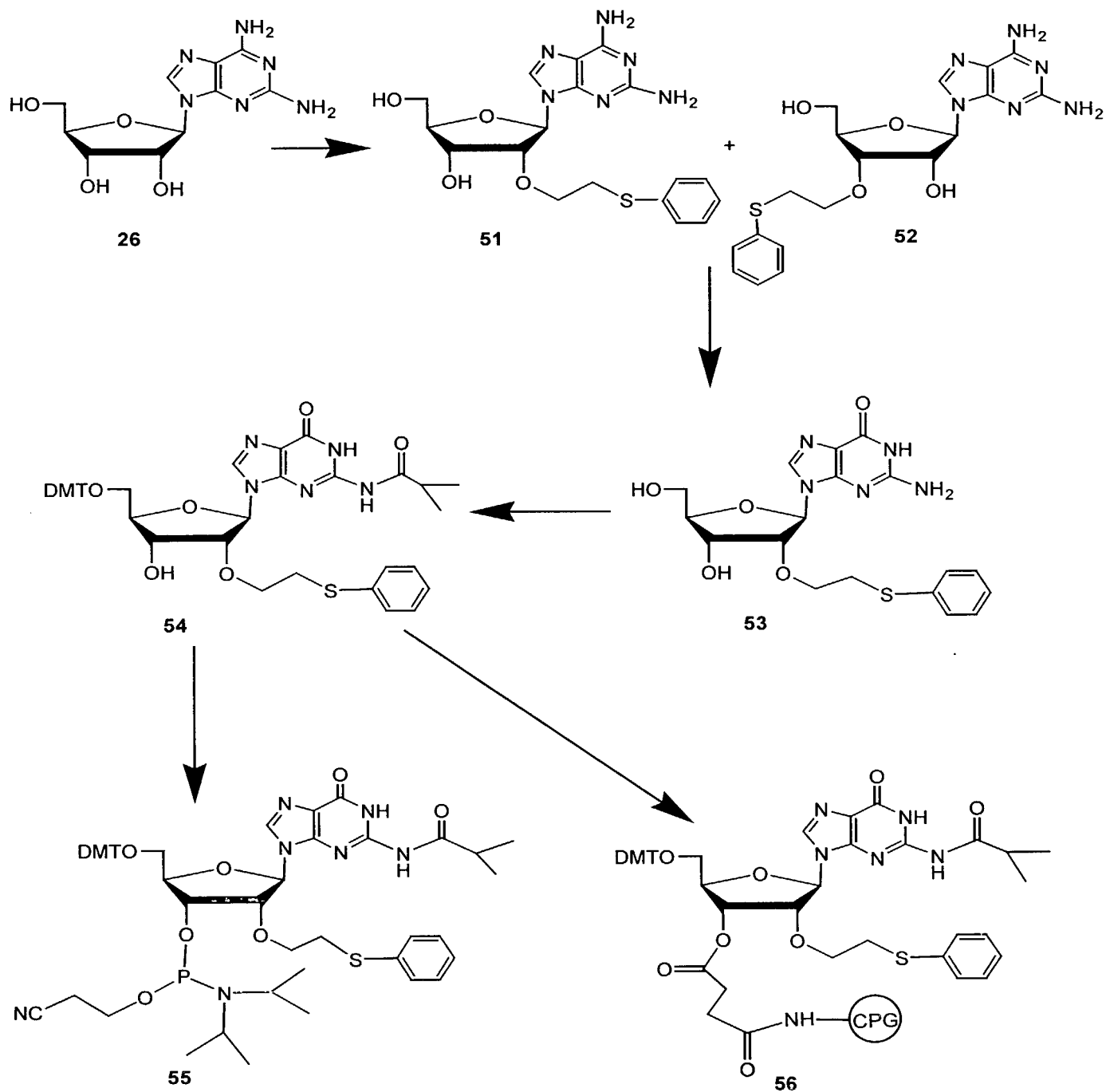




Figure 11

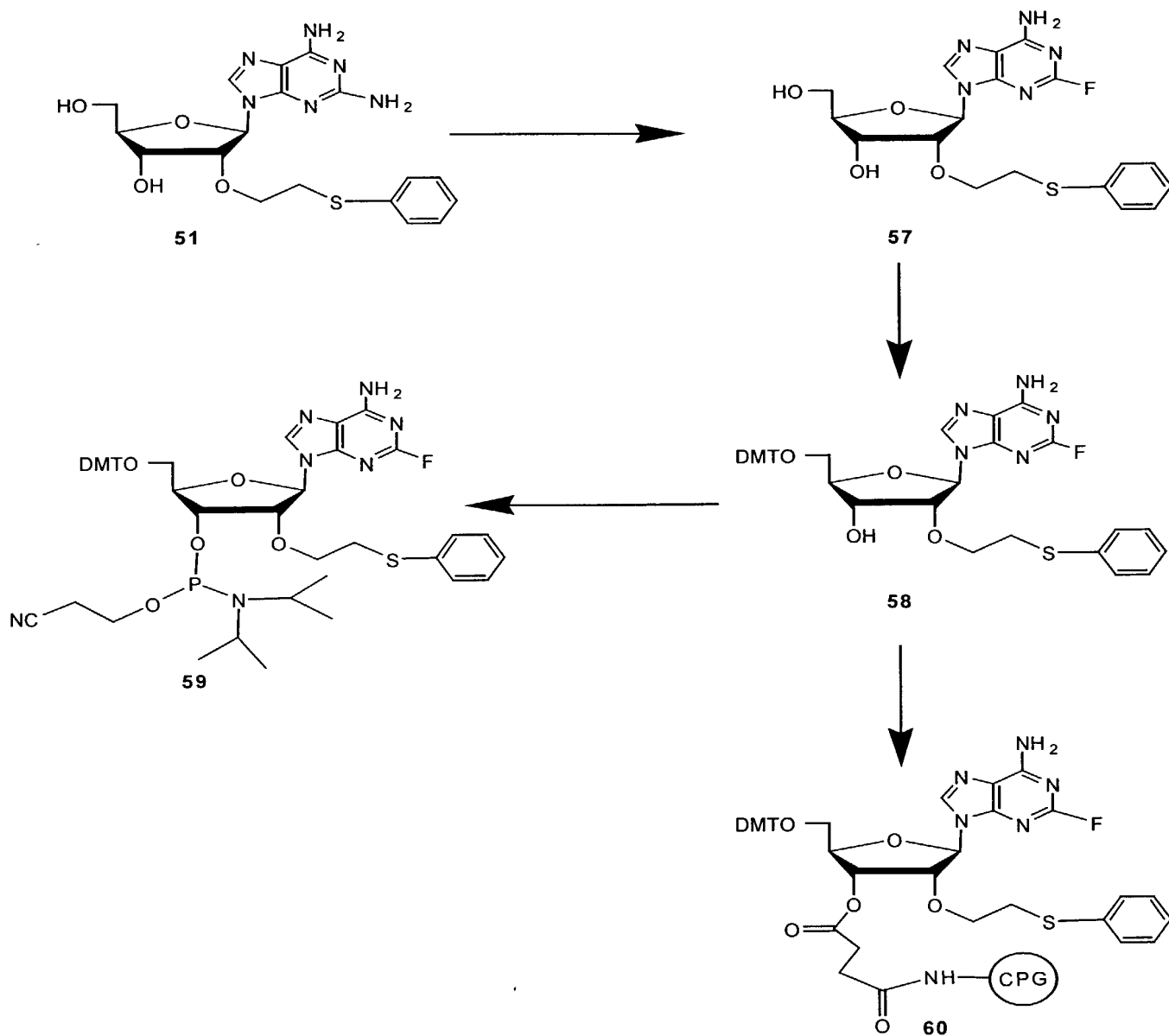
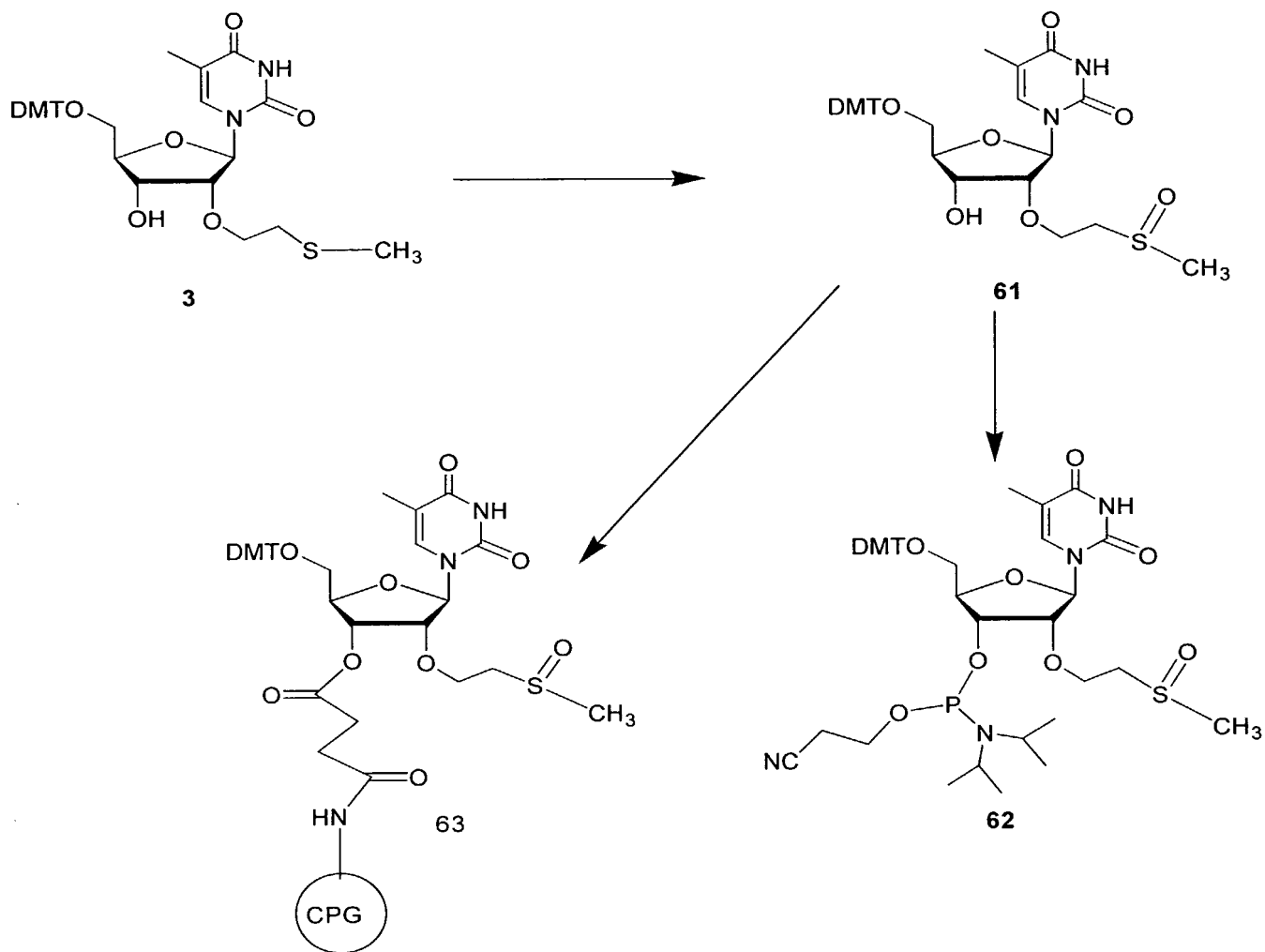
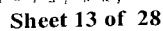




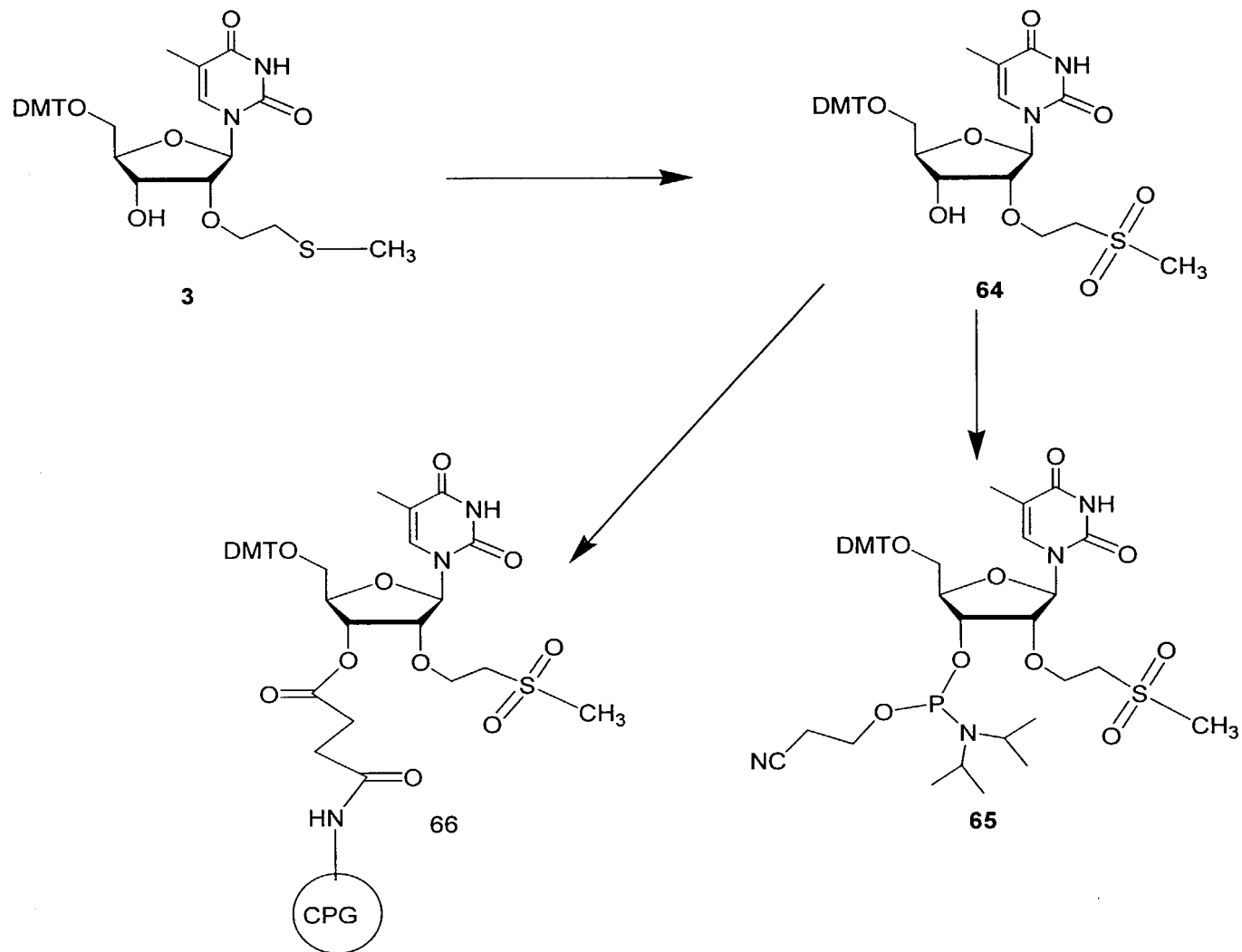
Figure 12





Inventors: Prakash and Manoharan

Filing Date: 1/28/02

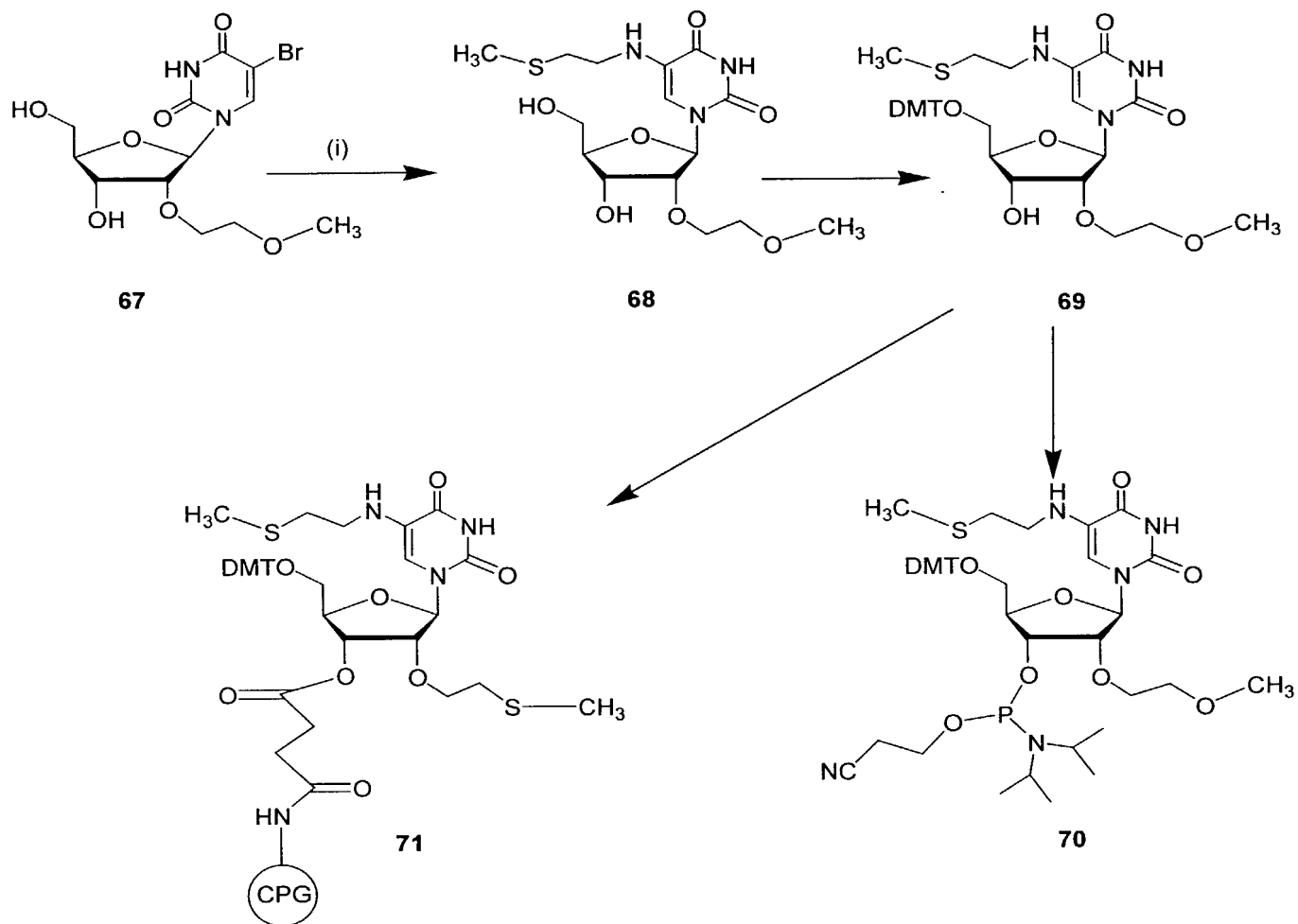




10/058,740, 08/12/02

Docket No.: ISIS-4853 Sheet 14 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N. 10/058,740 Filing Date: 1/28/02

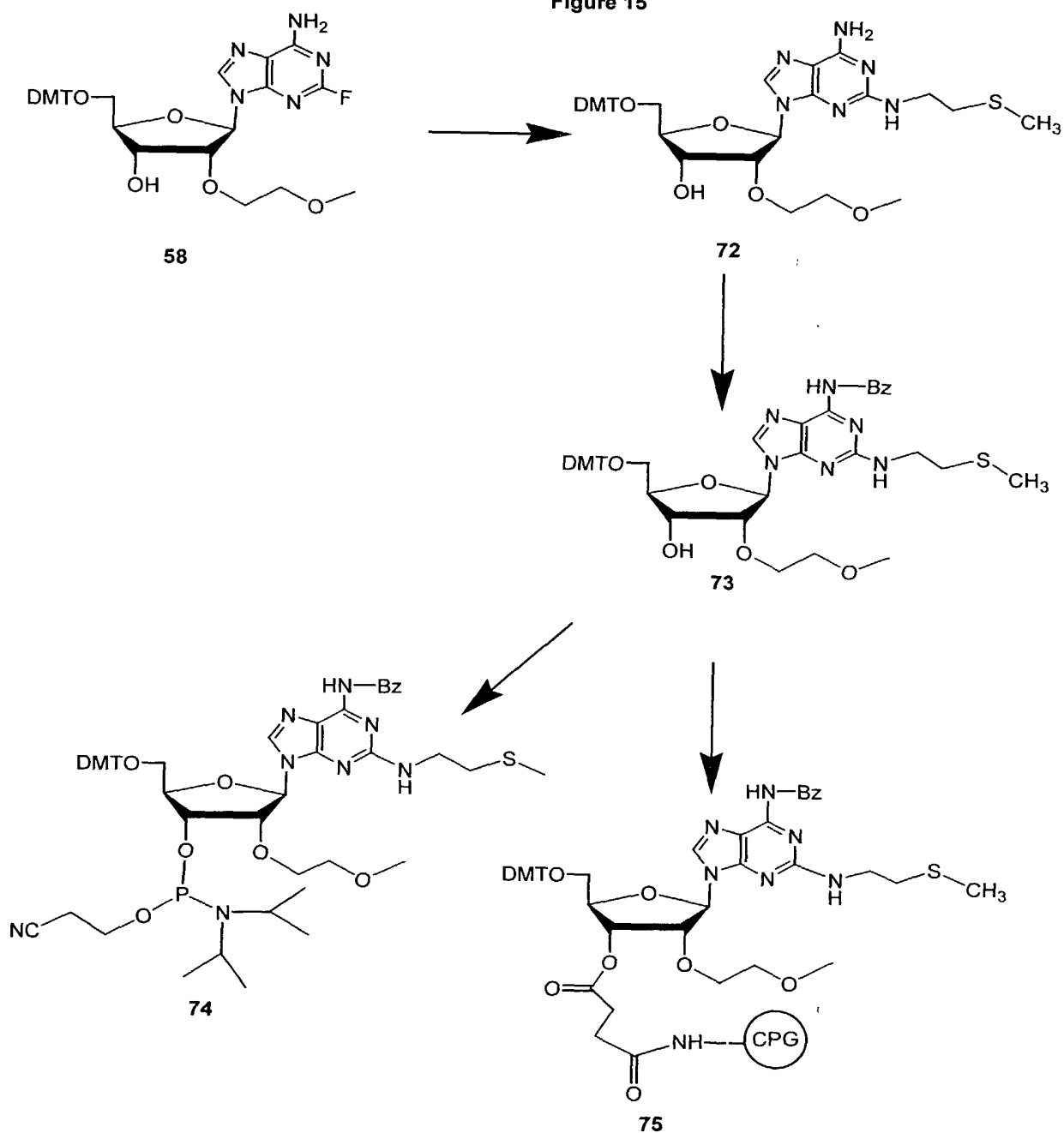
Figure 14





Docket No.: ISIS-4853 Sheet 15 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 15





2005053740, 08/12/02

Docket No.: ISIS-4853 Sheet 16 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 16

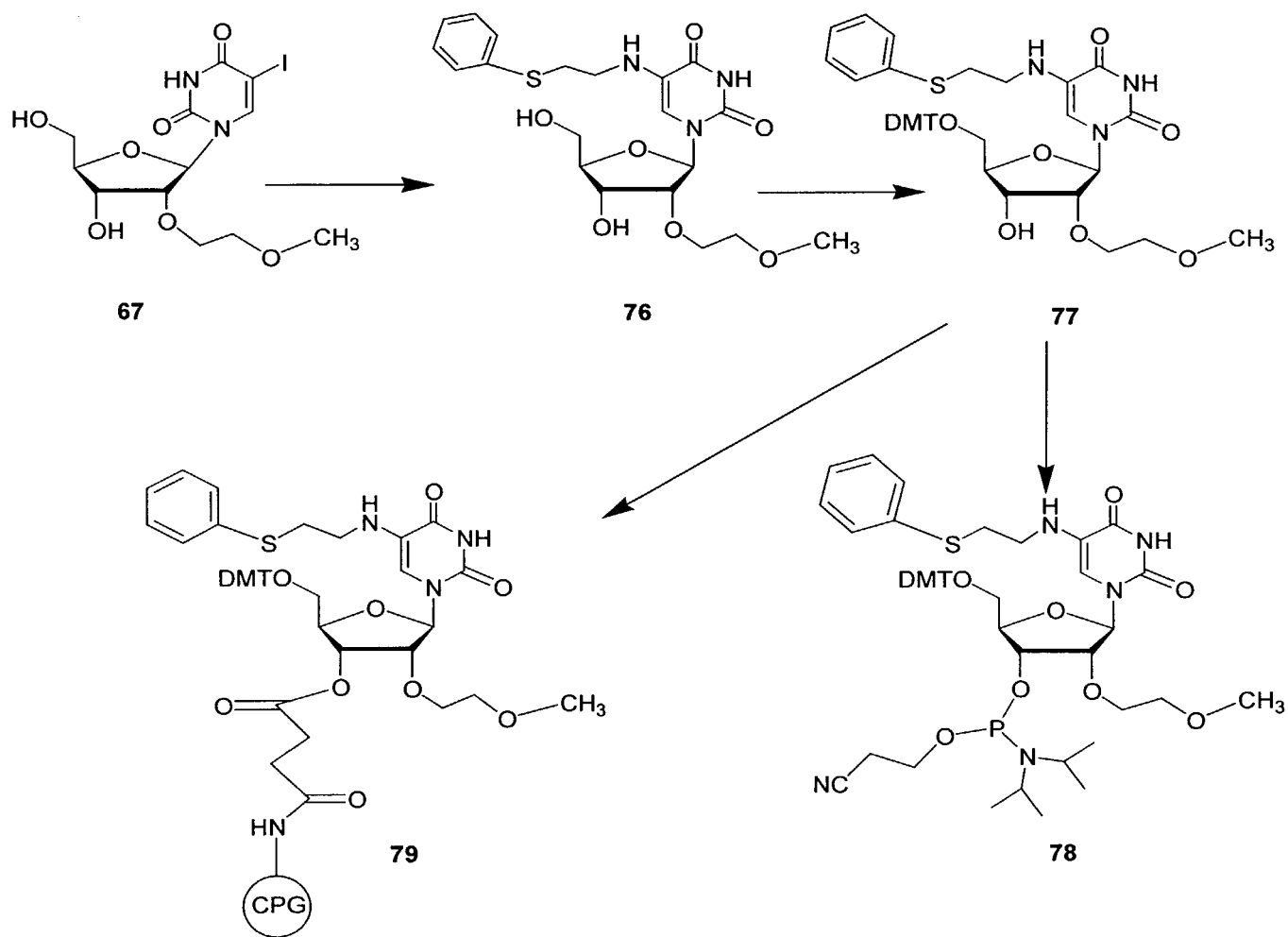
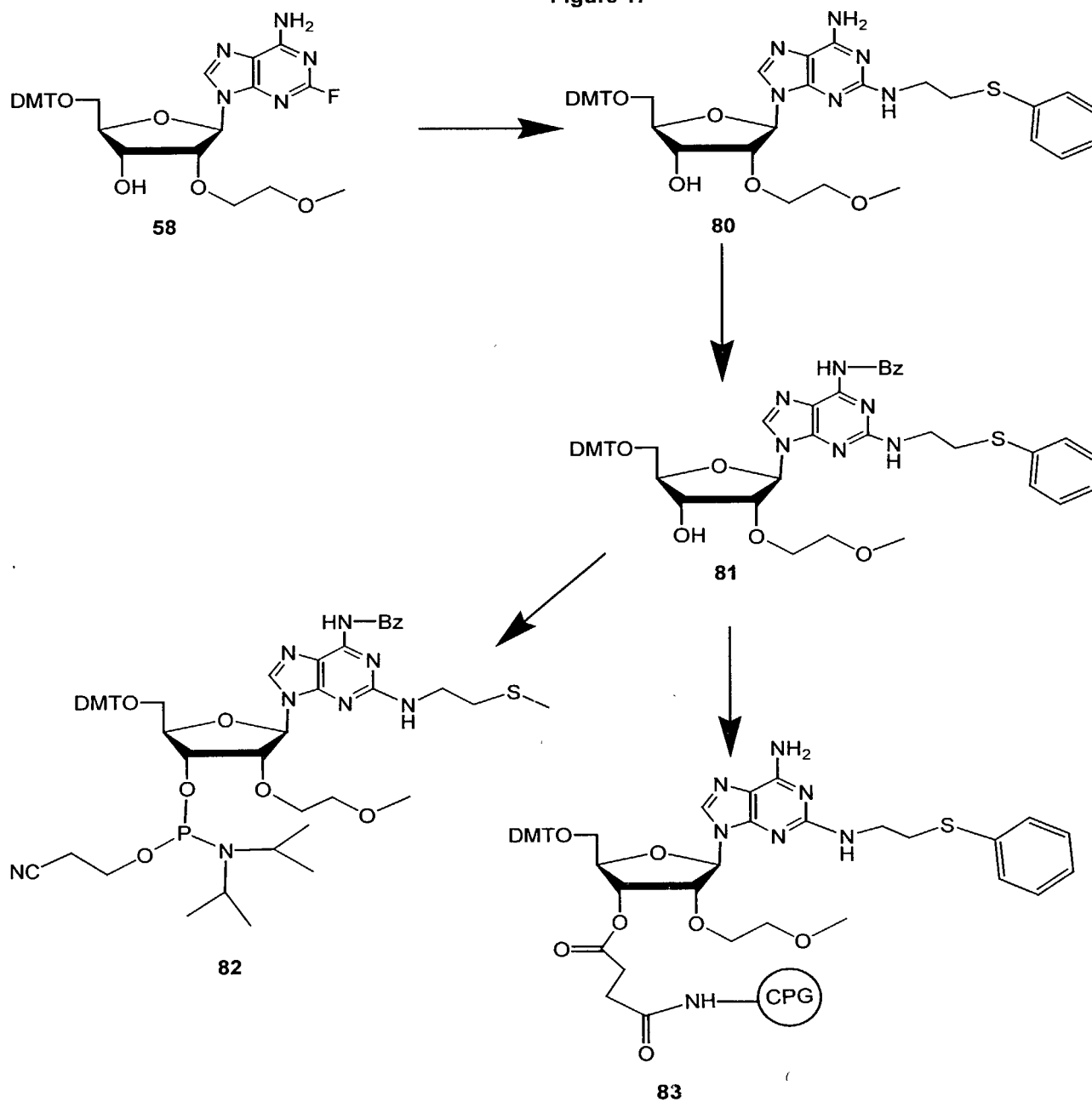




Figure 17

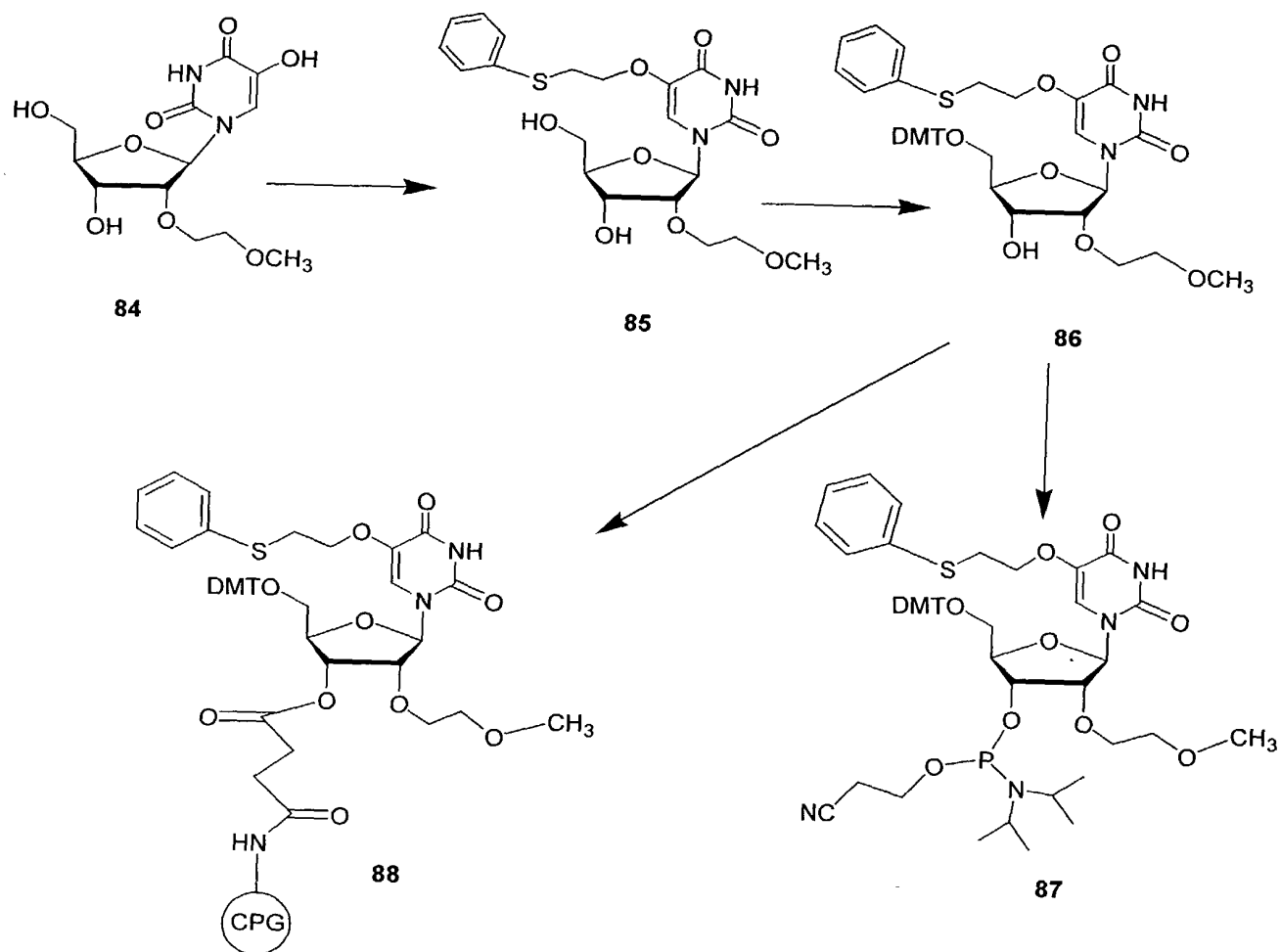




10/058,740, 08/12/02

Docket No.: ISIS-4853 Sheet 18 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 18





10/058,740, 08/12/02

Docket No.: ISIS-4853 Sheet 19 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 19

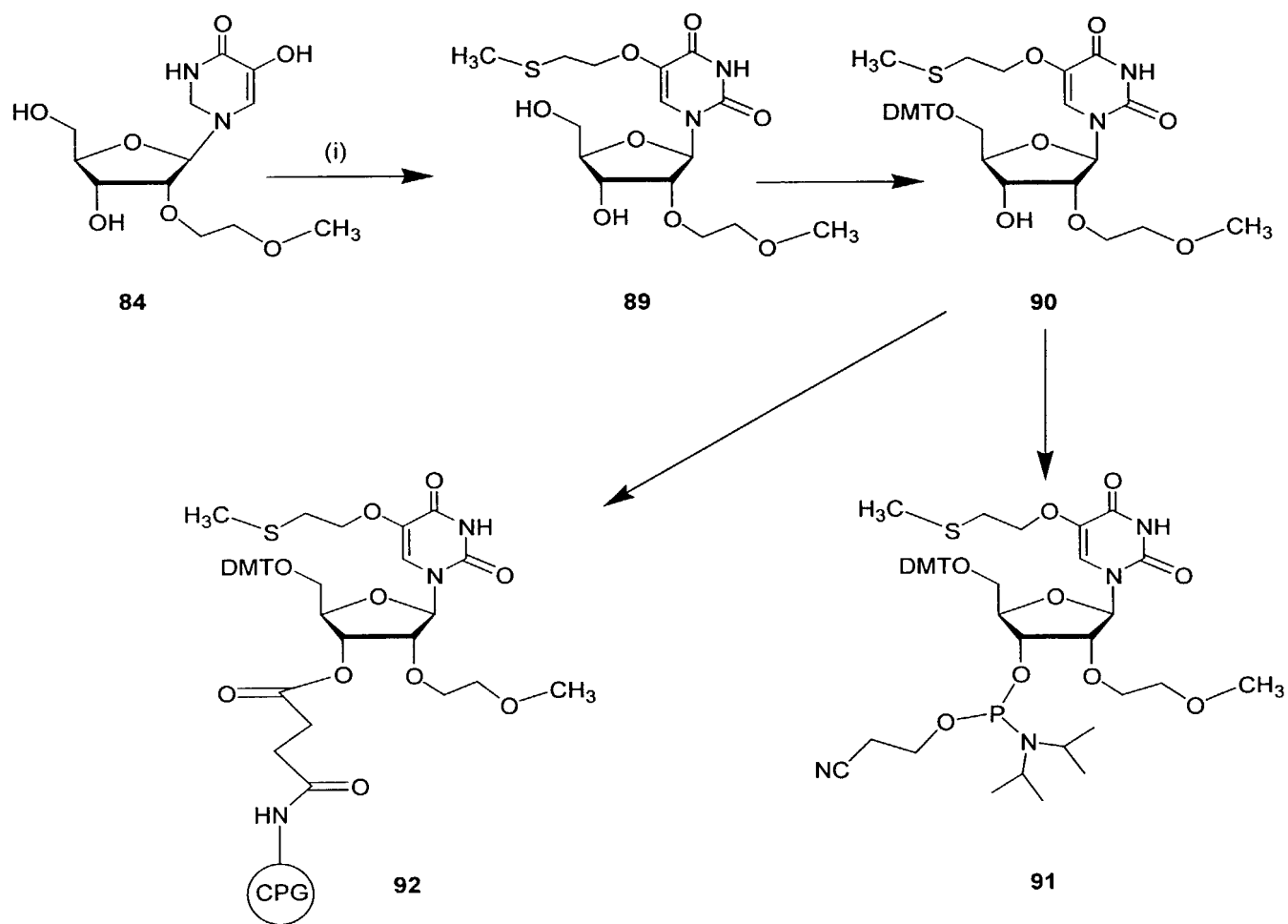
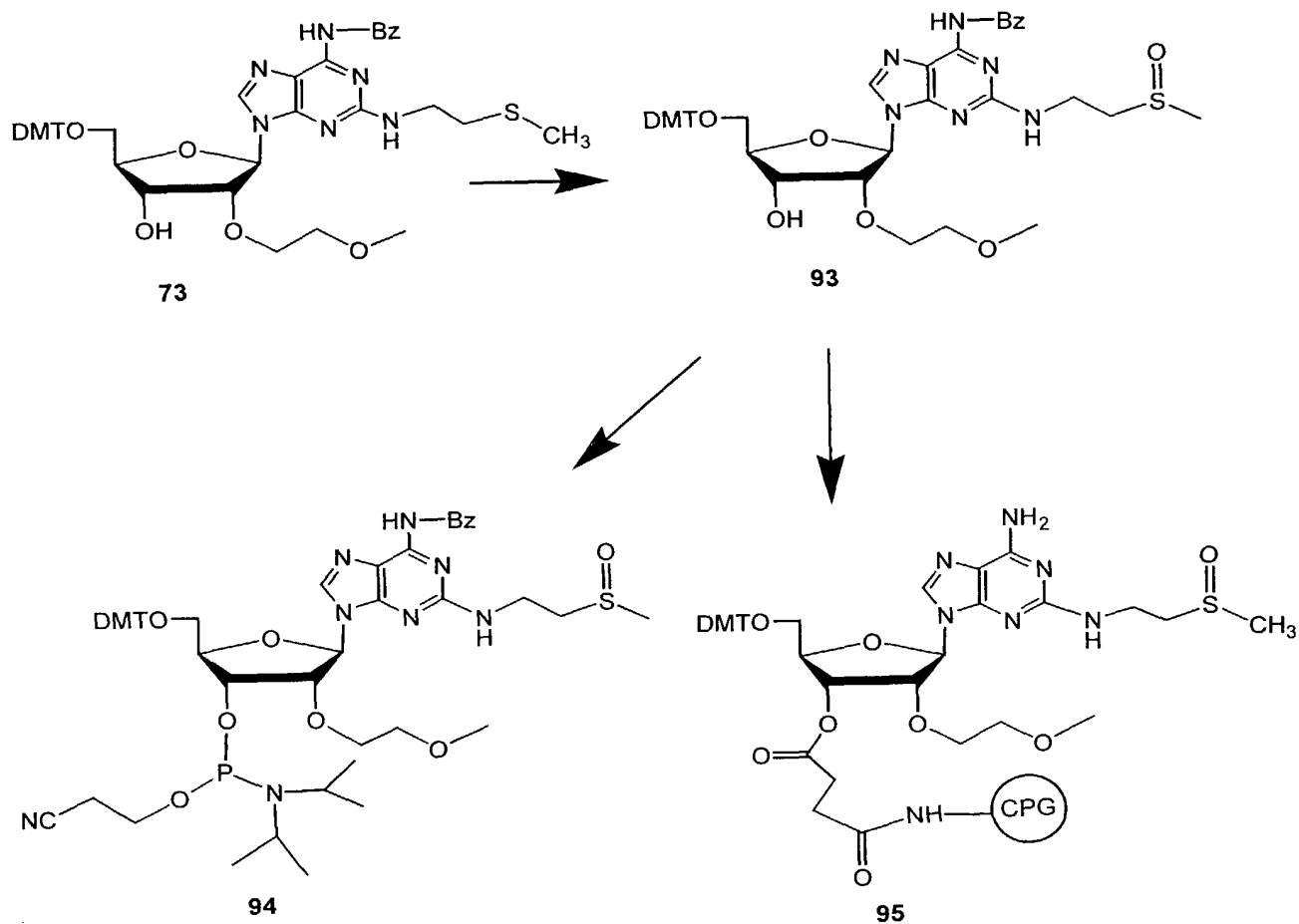




Figure 20

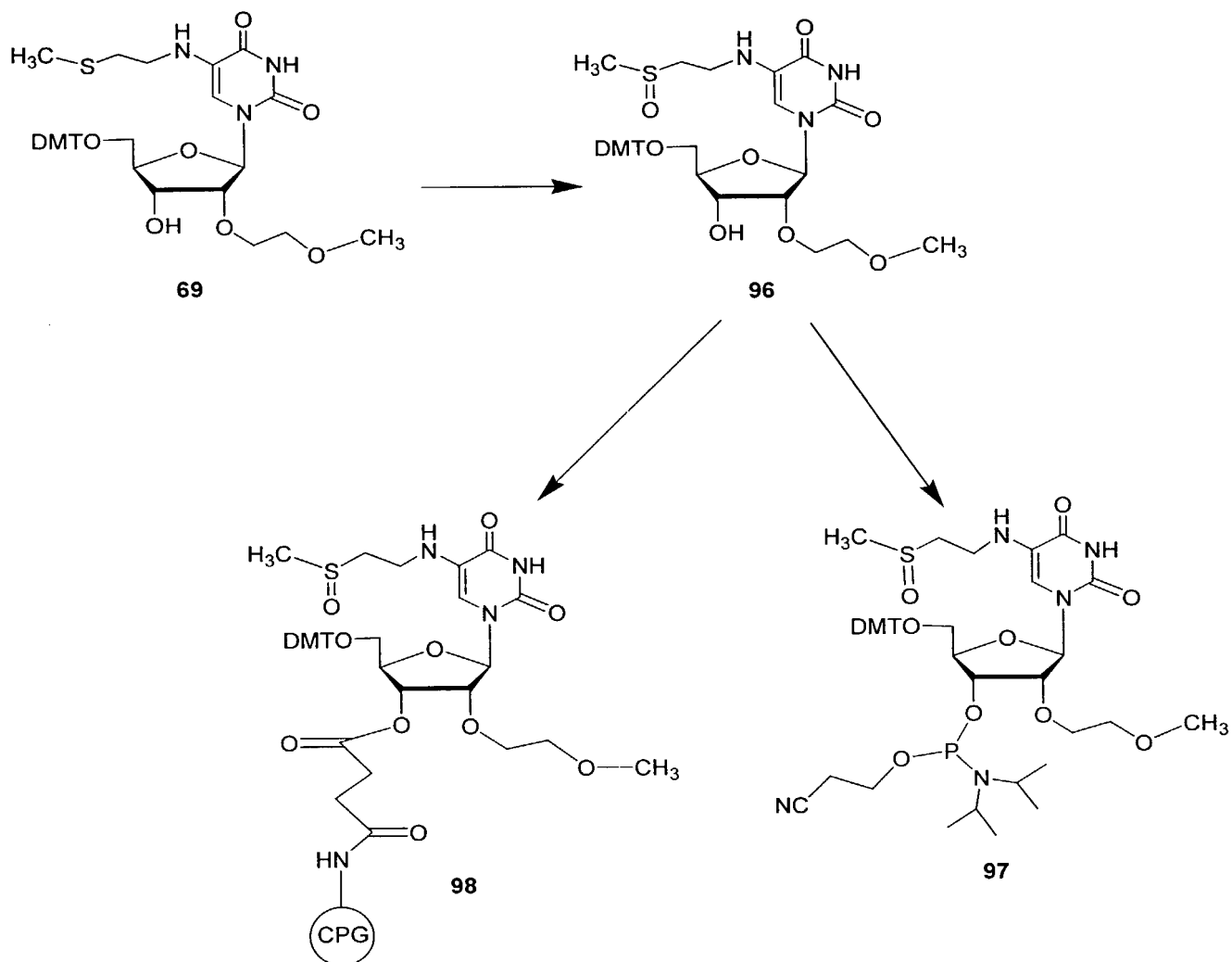




10/058,740, 003,1272

Docket No.: ISIS-4853 Sheet 21 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 21





10/058,740 - 03/2/02

Docket No.: ISIS-4853 Sheet 22 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 22

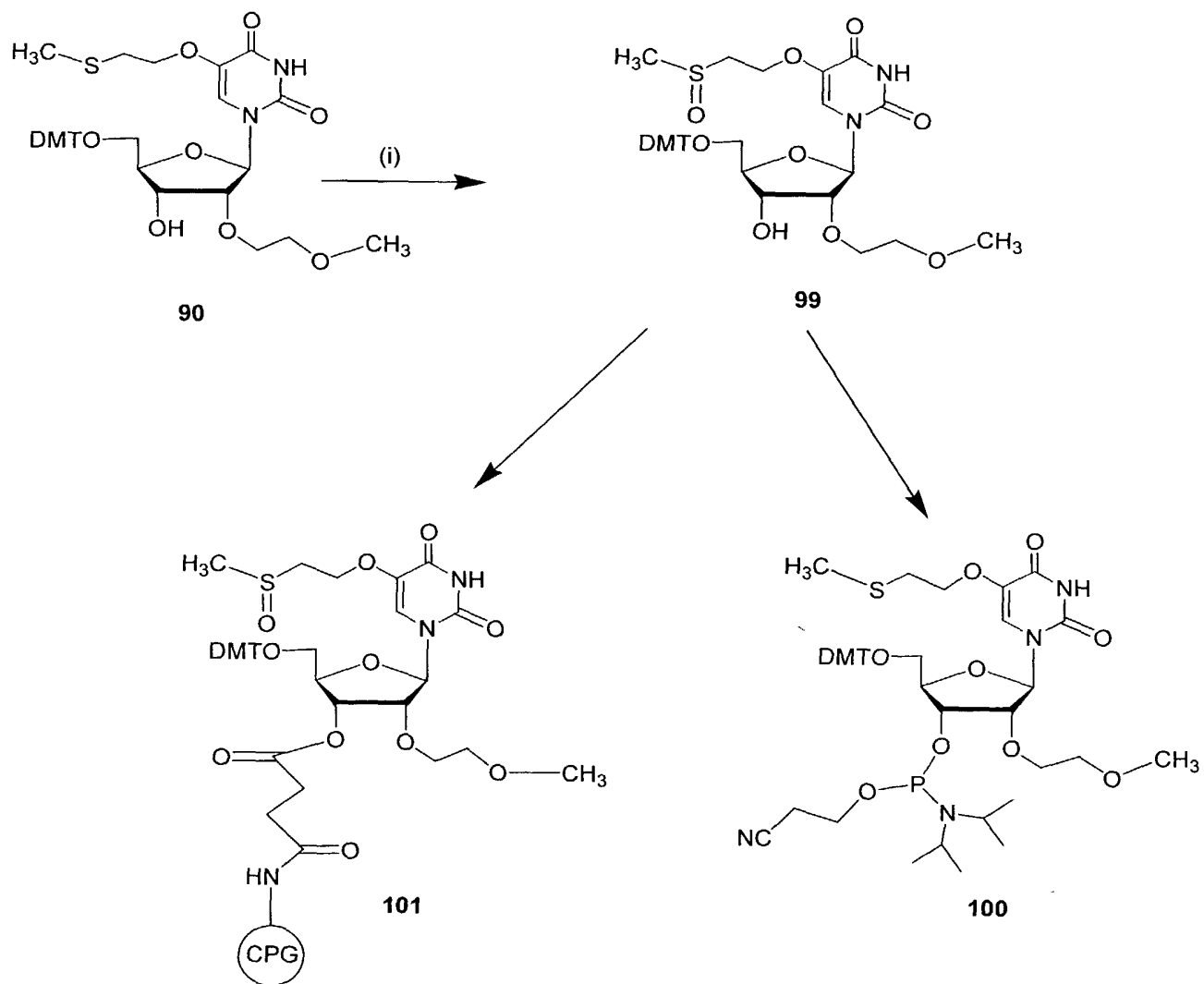
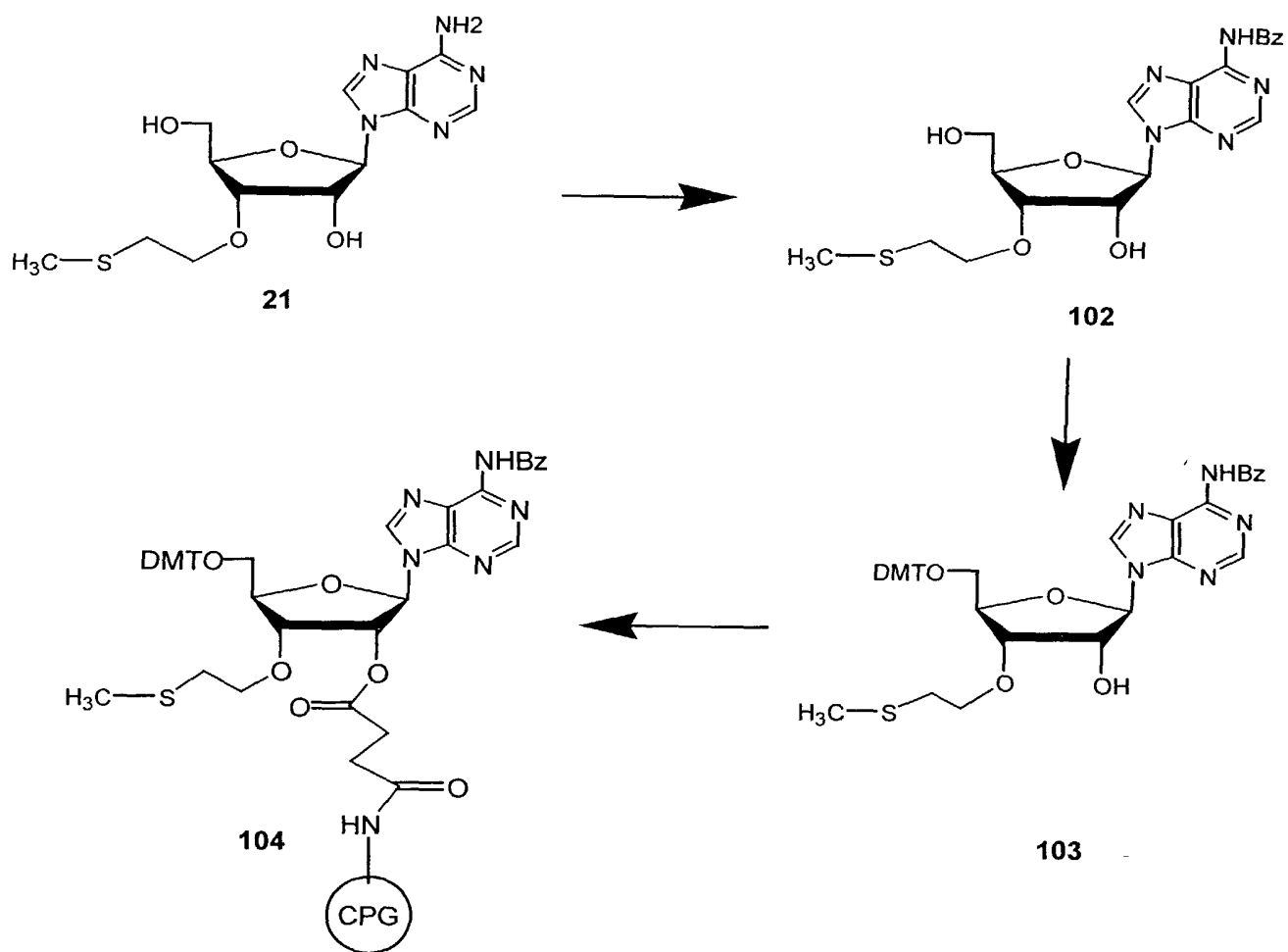




Figure 23

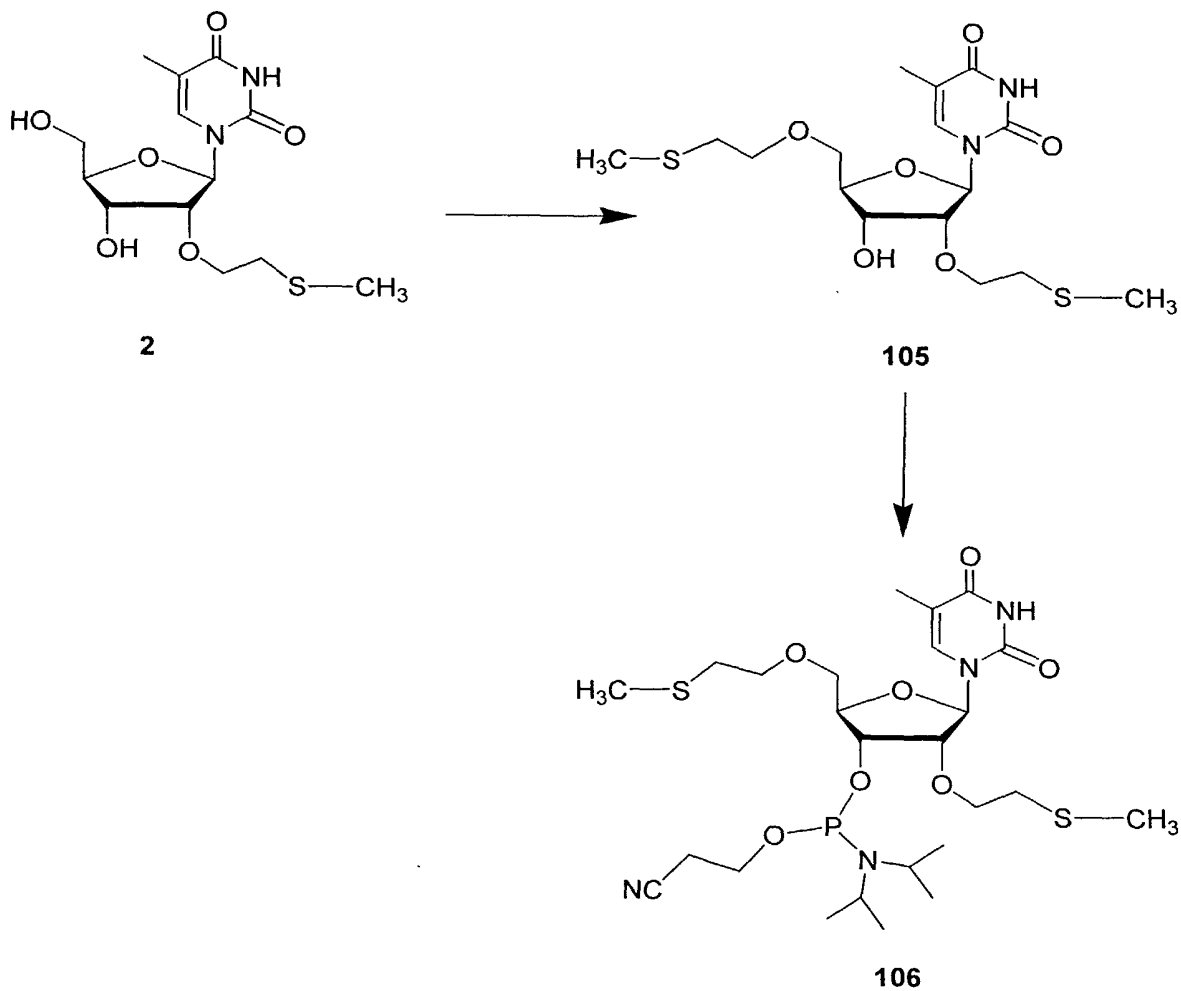




10/058,740, 000,000,000

Docket No.: ISIS-4853 Sheet 24 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

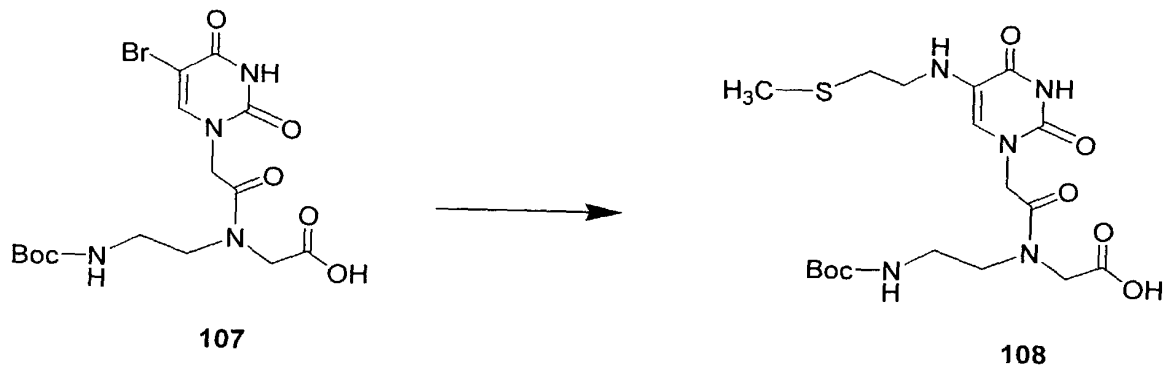
Figure 24





Docket No.: ISIS-4853 Sheet 25 of 28
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides
Inventors: Prakash and Manoharan
S/N: 10/058,740 Filing Date: 1/28/02

Figure 25





Docket No.: ISIS-4853

Sheet 26 of 28

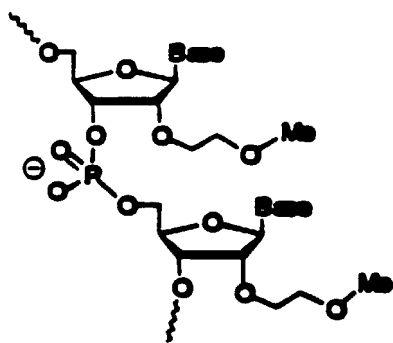
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides

Inventors: Prakash and Manoharan

S/N: 10/058,740

Filing Date: 1/28/02

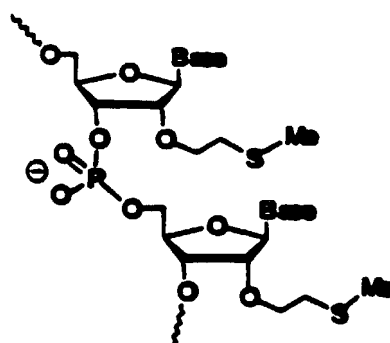
Figure 26



Z-OMOE: Z-O(2-Methoxyethyl)-RNA

$\Delta T_m = 2.0^\circ \text{C}$ (rel. to P=O)

No albumin binding with native
diester (P=O) backbone



Z-OMTE: Z-O(2-Methylthioethyl)-RNA

$\Delta T_m = 2.0^\circ \text{C}$ (rel. to P=O)

Low-affinity albumin binding with
native diester (P=O) backbone



Docket No.: ISIS-4853 Sheet 27 of 28

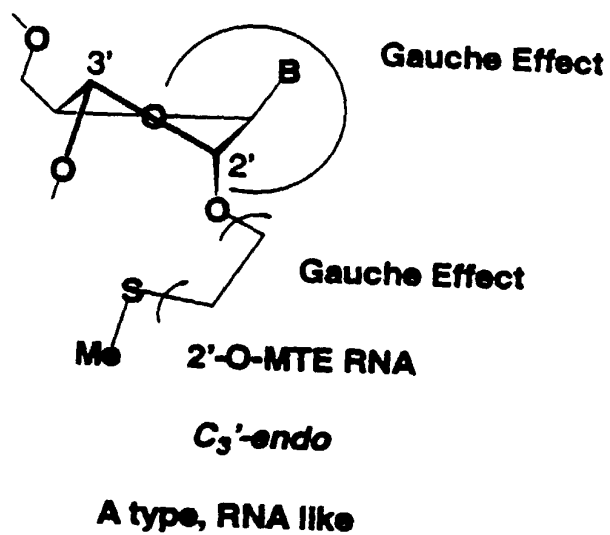
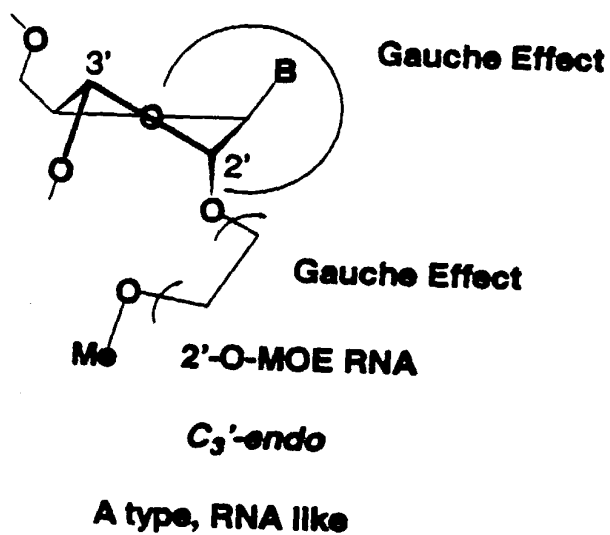
Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides

Inventors: Prakash and Manoharan

S/N: 10/058,740

Filing Date: 1/28/02

Figure 27





Docket No.: ISIS-4853

Sheet 28 of 28

Title: Methods of Modulating Pharmacokinetics
of Oligonucleotides

Inventors: Prakash and Manoharan

S/N: 10/058,740

Filing Date: 1/28/02

Figure 28

